From: Dr Paul Goldenheim
Sent: Tuesday, September 03, 1996 5:15 PM
To: Rufus Marsh; Dr. Brian Burke; Dr Robert Kaiko
Subject: Re: OC92-1001, clinical review

look like great suggestions

_____ Reply Separator _____
Subject: OC92-1001, clinical review
Author: Dr Robert Kaiko at NORWALK
Date: 8/30/96 5:12 PM

as in my clinical review of Kalso (-0303) you may find my review of the similar study (-0101 below) helpful towards further developing -0303

_____ Forward Header _____
Subject: OC92-1001, clinical review
Author: Dr Robert Kaiko at NORWALK
Date: 8/22/96 11:54 AM

EC, RR, MS:

We've got a fine start, but we need to do a lot more. Thanks, guys, for getting your comments back to EC well in advance of her timeframe.

Below I've first tried to present several points which apply to a number of different sections, but don't necessarily reiterate them when I review the specific section; I do this latter on as well. So, EC, I leave it to you to apply the necessary revisions where appropriate in many instances. At the end I provide my draft version of a summary conclusion fyi and consideration.

1. adjustment of Cmax and Cmin to 80mg oxy and 120mg ms

- the reason this was requested was to provide an additional was to look at treatment differences in variation (c.v.) as though as all patients received the same dosage of each treatment, but there was no discussion of which dosages the 2 products whould have their concentrations adjusted to

- while I understand how the choice was made to use 80 and 120 of oxy and ms, I'm not sure I would have chosen these dosages because they do imply that we believe this ratio to be equianalgesic, and I don't believe we have sufficient conclusive evidence that this is the case, whereas we do have better evidence that a 1:2 dose ratio is equianalgesic.

- we should not refer to this ratio as "equianalgesic"

- inspection of the dose adjusted plasma concentrations of the analytes suggest to me that the dose-adjustment was incorrectly calculated: in all cases the adjusted concentrations are higher than the unadjusted concentrations whereas 80mg oxy and 120mg ms are lower than the doses actually administered. I might be wrong if there were some outliners who really had a very different relationship between dose and concentration compared to most patients. Another possibility is that the means are mislabeled, I suppose. Regardless, it needs to be checked and if they were miscalculated I would suggest not redoing the calculations because it is a "long shot" for really providing

additional insight into the data.

If they were correctly calculated and we decide to leave them in the report, the apparent discrepancy requires evaluation and explanation in the report.

- were inferential statistics only applied to "adjusted" Cmax and Cmin values? - this may need to be considered in deciding what to do.

2. c.v. should be used as a measure of "variability" where as the scaled difference is a measure of "fluctuation"

3. scaled difference: this is a measure of "fluctuation" and might be best refered to as such as the latter is a more commonly used term; I would include in the summary tables the actually fluctuation values (and level of significant difference) along with the Cmax and Cmin.

4. the significant treatment difference in the dose-concentration relationship is an important one: with correlation coefficients of 0.72 for oxy and 0.32 for ms, resulting coefficients of determination are 0.5 and 0.1 respectively. This means that half the variation in oxycodone concentration is directly accounted for by differences in dose whereas only one-tenth of the variation in morphine concentration can be attributed to dose differences. This relates to our contention that OxyContin provides more consistent and predictable therapeutic drug concentrations.

5. FACT-G results should be considered for rewriting once we have a better handle on what they mean.

6. mean number of dose adjustments: we should not be using the mean in this situation of highly skewed distributions of data which do not fit a normal distribution; in this case we should use the median and/or mode as a more valid measure of central tendency, otherwise it is quite misleading to the reader.

7. "ratio of 1.5 planned for initial dose conversion": if this was the case (and I don't recall, but was under the impression that we used a 2:1 ratio), then we need to explain that at the time the study was designed, we were using the ratio suggested in the literature by the Kalso study rather than the ratio of 2:1 suggested by the earlier literature and more recently confirmed in our own relative potency study; if the primary reason for using the ratio for initial (as well as subsequent conversion) was related to clinical supply/blinding/ packaging issues (which may have been the case - SEE protocol - then we need to make that very clear. If we did use an initial conversion of 2:1 the language needs to reflect that and we also need to deal with the use of 1.5 in this report/study (eg, dose adjustment ratio; clinical supply issues such as availability of tablets strengths in a 1.5 ratio and blister cards with an overall 1.5 ratio as well).

8. pk/pd: other than merely saying there was no strong relationships we should mention the treatment differences oberved in the correlation between plasma drug and pain intensity: wasn't the relationship significant for oxy but not for ms? The summary and section 3.7.6.1 don't distinguish between treatment and Table 20 should have the statistically significant relationships identified somehow. Doesn't the data tell us that, while (granted) there are no strongly predictive pk/pd relationship here, the relationships between plasma oxycodone and analgesia (as well as, perhaps, other effects) are more commonly significant than those between morphine and its effects? I need to look at the appendices more and contribute more concretly here.

9. safety

- while there were no oxy patients with hallucinations and 2 ms patients with hallucinations, this needs to be pointed out in the summary and other text because of the significance of this in light of

other studies. Kalso reported a similar difference as well as others and it has become a point of considerble interest.
- while the daily risk ratio can stay as it has been calculated and presented I need point out that I had intented this to be calculated separately for each of the common opioid effects.
- because OxyContin is the test drug and MS Contin, the reference, it would be more appropriate to "always" use language which reflects this (eg, the higher incidence of "severe" adverse experiences with ms should discussed in terms of a lower incidence with oxy - by the way, maybe I missed it in the text, but is the difference statistically significant?)

pg54, 3.7.8.4

what about including patients with renal and hepatic labs that were indicative of relatively poor function, if any?

pg55, 3.8
perhaps some revisions and additions here

10. Fig 7 - can the level of sig. be added to the figure; depending on the sig, we may need to discuss the inverse relationship between morphine concentration and analgesia.

11. pg 26, 3.2
-1st bullet: replace "variation in....." with "fluctuation." [period]
-2nd bullet: OK
-last bullet: don't bother

12. pg 27, 3.3.2
- 1st paragraph, 5th line: on the average, steady-state is attained in a day with both drugs.
- 1st paragraph, Tmax: from study to study of both drugs there's slight differences in Tmax such that the use of these very specific values and their apparent difference may be misleading; I would remove this as is and merely state that Tmax is approximately 3 hours for both.
- 1st paragraph, next to last sentence: rather than "conversion between" we should say "conversion from oxycodone to morphine"
- 2nd paragraph: why is this in this section? its less of a rationale/ design issue than it is a double-blinding issue, except for the fact, however, that it may have contributed to the use of the 1.5 ratio - so merely make more explicit in that regard.

13. pg 31, second bullet and next full paragraph: if tricyclic antidepressants were being used as adjuvant analgesic therapy were such patients excluded, or the agent removed or what?

14. pg 33, 3.3.7.2.3, MSDEQ
why the Jasinski reference?

15. pg 34, 3.3.8
this says nothing about morphine or any of the metabolites of either drug.

16. BUN, creatinine, SGOT, SGPT, and bilirubin where appropriate, we need to discuss these as they relate to renal and hepatic function and how, over the wide range (what were the ranges) of values there was little evidence of differences in the drugs or metabolite concentrations except in the case of morphine-3- glucuronide, which was elevated with chemistries indicative of poorer renal function (if we all agree that this is what the data shows). We need to make the case that this study provides reasonable evidence that oxy is not significantly vulnerable to poorer renal and hepatic function as in some cancer patients represented in this study. This needs to be in the summary as well.

17. pg 42
-2nd paragraph: if the gender and age differences were not sig then they should not be mentioned

18. "itchy" and "scratching"
this treatment difference is important: these are the only MSDEQ treatment differences and they are ones which validate each other: "itchy" as reported by patients and "scratching" as independently observed by the investigator supports a real drug difference.

19. pg 46, 2nd paragraph; is this noted in the summary. I think its important to take baseline into consideration.

20. 3.7.6.2
-table: which treatment?

21, 3.7.6. Yes, we need more interpretation here. I will contribute more specifically after I get my hands on the appendices again.

22. pg49, 3.77
-1st paragraph, 7th line: replace "variation" with "fluctuation" here and etc.
-1st paragraph, last line: strike "at equianalgesic doses -2nd paragraph: as per item #4 above
-2nd paragraph: yes, the "bioavailability" statement is correct and may be following by something like: "Drugs with high oral bioavailability (eg, oxycodone) are thought to have less variation in the extent of their aborption relative to those with lower bioavailability (eg, morphine). This has been previously demonstrated for OxyContin relative to MS Contin in normal volunteers (citation of study on file). Both the rate (ie, Cmax) and extent (ie, AUC) of drug absorption were significantly less variable with OxyContin."
-2nd paragraph: separate out the BUN etc discussion into a separate paragraph and add clinical signficance of observations as per #16 above.
-3rd paragraph: I will elaborate after more review of appendices. -5th paragraph: replace "mean number of dose adjustments" as in #6 above

23. Table 5.3
-if this analysis was not called for in the original protocol I would question the need to include it as it gives too much credence to the ratio of doses as being equianalgesic; given the biases (see item #7) as well as lack of study design/controls that are necessary to establish equianalgesic doses, I would provide the descriptive statistics only and drop the ratio and the limits.

24. Table 9,
- see item #3 above regarding adjusted concentrations

25. Table 9,
- see items #1 and #3 above

26. Table 10
- strike section relating to use of "log" calculations; it's not an appropriate way to related concentration to dose.

27. Table 14.2
- Is any explanation or discussion appropriate to develop to deal with the apparently greater efficacy of ms reflected in these tables?

28. Table 20
- see item #8 above and add asterisks as in Table 25.

29. summary "Conclusion", bk draft version:

"While there were no difference in variation in the peak concentrations or in the trough concentrations, the peak/trough fluctuation was a third less with CR oxycodone than with CR morphine. In addition, whereas 50% of the variation in plasma oxycodone concentrations could be attributed to differences in oxycodone dosages, only 10% of the variation in plasma morphine could attributed

to differences in morphine dosages. These observations are consistent with the greater consistency and predictability of CR oxycodone in providing therapeutic opioid concentrations.

Whereas there was little evidence of any association between various measures of hepatic or renal function and the plasma profiles of oxycodone and its metabolites, noroxycodone and oxymorphone, consistently significant associations were observed between measures of
relatively poor renal function and concentrations of the active metabolite of morphine, morphine-6-glucuronide. This suggests that oxycodone may be preferred over morphine in patients with relatively poor renal function.

CR oxycodone provided comparable efficacy as CR morphine with no significant differences in: number of dosage adjustments; time to stable pain control; degree of pain control; use of rescue medication. While, overall, adverse reactions were comparable, patients receiving CR oxycodone reported less itching and the investigators independently observed less scratching among patients receiving CR oxycodone as compared with CR morphine patients. This provides clinical significance to the previous report of less histamine release with oxycodone as compared to morphine. As is interesting in light of earlier reports of fewer hallucinations with oxycodone than with morphine, there were no patients who experienced hallucinations with CR oxycodone as compared to two CR morphine patients who experienced hallucinations in this study. Thus, while the safety profile of CR oxycodone was comparable to that of CR morphine, there are minor differences which favor CR oxycodone.

While CR oxycodone was comparable to CR morphine in respect to efficacy, there were differences in clinical pharmacokinetics, in general, and in patients with signs of poor renal function which favor CR oxycodone. Similarly, while the safety profiles were comparable, minor differences favor oxycodone.

Overall, CR oxycodone provides a comparable therapeutic profile as CR morphine."